ANTIPHOSPHOLIPID ANTIBODY AND LUPUS ANTICOAGULANT

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National Institute of Arthritis and Musculoskeletal and Skin Diseases
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PURPOSE

The Arthritis Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports research on the autoantibodies found in patients with systemic lupus erythematosus. The Thrombosis and Hemostasis Branch of the National Heart, Lung, and Blood Institute (NHLBI) supports research on hypercoagulability and thrombosis. The NIAMS and the NHLBI, through this program announcement, encourage the submission of grant applications for basic and clinical research related to antiphospholipid antibody and the lupus anticoagulant.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This program announcement, Biology of Autoimmune Antiphospholipid Antibody and Lupus Anticoagulant, is related to the priority areas of health promotion: maternal and infant health and heart disease and stroke. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by foreign and domestic, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State or local governments, and eligible agencies of the Federal government. Applications from minority individuals and women are encouraged. Foreign institutions are not eligible for the K awards.

MECHANISM OF SUPPORT

Investigators may apply for research project grants (R01), First Independent Research Support and Transition (FIRST) awards, (R29), and career development (K04, K08, K11) awards.

RESEARCH OBJECTIVES

Background

Autoimmune antiphospholipid antibody and lupus anticoagulant, two closely related antibodies, are associated with a clinical syndrome consisting of recurrent thromboocclusive disease, livedo reticularis, and repeated in utero fetal deaths. Many persons with this antibody do not have systemic lupus erythematosus and some are apparently well. Among persons with clinical illness attributable to antiphospholipid antibody, there is considerable heterogeneity of symptoms and of antibody characteristics. The mechanisms by which clinical events occur are unknown. A serum cofactor, apolipoprotein H, is generally required for the binding of autoimmune antibody to phospholipid in the most commonly used solid phase assay, but precise knowledge concerning the physical nature of the antigen and the relevance of the cofactor in antibody binding is still lacking. Animal models for the antibody and for the syndrome do not currently exist. Although anticoagulation with drugs, such as aspirin or warfarin, are frequently used for treatment, there is as yet no uniform regimen for all clinical conditions associated with the antibodies and no definitive clinical trials have yet been conducted.

On September 25, 1991, the NIAMS and the NHLBI co-sponsored an Antiphospholipid Antibody/Lupus Anticoagulant Workshop. This Workshop identified research issues that form the basis of this program announcement. These issues include: the nature of the relationship between antiphospholipid antibody and lupus anticoagulant; the roles of apolipoprotein H and of other phospholipid binding proteins in antibody binding and in clinical illness; the chemical or structural nature of the antigen or epitope; the (presumably) exogenous trigger for induction and maintenance of antiphospholipid antibody in patients; the reasons for patient heterogeneity; and

the construction of animal models. Treatments for the various clinical manifestations of the syndrome comprise an additional question.

Research Goals and Scope

The primary goal of this program announcement is to foster research that enhances knowledge about mechanisms of action of antiphospholipid antibody. This goal includes, but is not limited to, studies that integrate multidisciplinary approaches.

The scope of possible research areas includes, but is not limited to, the following topics:

o Studies of phospholipid structure relevant to antigenicity;

o Studies of the interaction of phospholipid-binding proteins, including annexins and antiphospholipid antibodies, with phospholipids;

o Studies of the induction and/or maintenance of antiphospholipid antibody;

o Studies defining the differences and/or similarities between antiphospholipid antibody and lupus anticoagulant;

o Elucidation of the mechanisms by which lupus anticoagulants and phospholipid antibodies promote hypercoagulability and thromboembolic events;

o Studies of the pathophysiology of fetal death associated with antiphospholipid antibodies;

o Animal models;

o Clinical studies, including differences and/or similarities between patients with systemic lupus erythematosus and those with primary antiphospholipid antibody syndrome;

o Treatment trials.

Investigators are encouraged to use the full range of current disciplines and techniques available to them.

STUDY POPULATIONS

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH and ADAMHA policy is that applicants for NIH/ADAMHA clinical research grants and cooperative agreements are required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis must be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information must be included in the form PHS 398 in Section 2, A-D of the Research Plan AND summarized in Section 2, E, Human Subjects. Applicants/offerors are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (i.e., Native Americans (including American Indians or Alaskan Natives), Asian/Pacific Islanders, Blacks, Hispanics). The rationale for studies on single minority population groups must be provided.

For the purpose of this policy, clinical research is defined as human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including but not limited to clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the United States' populations, including minorities.

If the required information is not contained within the application, the review will be deferred until the information is provided.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed AND the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

APPLICATION PROCEDURES

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may want to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC Program Director or Principal Investigator must be included with the application.

Applications are to be submitted on the grant application form PHS 398 (rev. 10/88) (applications submitted after May 1 are to use the PHS 398 (rev 9/91)) and will be accepted at the standard application deadlines as indicated in the application kit.

Application kits are available at most institutional business offices and may be obtained from the Office of Grants Inquiries, Division of Research Grants, Westwood Building, Room 449, National Institutes of Health, Bethesda, MD 20892, telephone 301/496-7441. The title and number of the announcement must be typed in Section 2 on the face page of the application.

The completed original application and six legible copies must be sent or delivered to:

Division of Research Grants

National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

REVIEW PROCEDURES

Applications will be assigned on the basis of established Public Health Service referral guidelines. R01 and R29 applications will be reviewed for scientific and technical merit by study sections of the Division of Research Grants, NIH. Initial review of applications for the K series will be by the review group of the relevant Institute or Center in accordance with the standard NIH peer review procedures. Following scientific/ technical review, the applications will receive a second-level review by the appropriate national advisory council.

AWARD CRITERIA

Applications will compete for available funds with all other approved applications assigned to that ICD. The following will be considered making funding decisions:

o Quality of the proposed project as determined by peer review

o Availability of funds

o Program balance among research areas of the announcement.

INQUIRIES

Written and telephone inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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Direct inquiries regarding fiscal matters to:

Diane M. Watson
Grants Management Officer
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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Numbers 93.846, Arthritis, Musculoskeletal and Skin Diseases Research and 93.839, Blood Diseases and Resources Research. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and

285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

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